

Draw Pharmacology *in your mind*

Autacoids

HISTAMINE

SEROTONIN

NITRIC OXIDE

ANGIOTENSIN II

EICOSANOIDS

If you are a pharmacy student
If you are postgraduate and want
to revise pharmacology by an
easy way
If you are using any pharmacology
reference
this file will aid you
> And wait for more <

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لا تنسوني من صالح دعائكم

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VISIT...

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AUTACOIDS

Local hormones
(different from classical hormones)

Properties

1. Synthesized at site of action
2. Mainly they are acting locally but can lead to generalized effects if over secreted
3. Not stored nor released from glands

Classification

1. Biogenic amines ex. Histamine - 5-hydroxytryptamine (5HT)
2. Vasoactive polypeptides ex. Angiotensin II - Kinins - Substance P
3. Membrane derived lipids ex. PGs (prostaglandins) - LTs (Leukotrienes) - TXA₂
4. Endothelial derived active substances ex. NO (Nitric Oxide) - Endothelin

1. Histamine

1) Synthesis

Histidine (amino acid) $\xrightarrow{\text{Histidine decarboxylase}}$ Histamine

2) Abundance

- Histamine is mainly found in **lungs**, **skin** and **GIT**
- **At cellular level, it is found in :**
 1. **Mast cells** and basophils
 2. **In GIT** it is found in specialized cells called **histaminocytes** → which exists at the acid secreting cells in the stomach (Parietal cells)
 3. It is also found in the **brain** and acts as a **neurotransmitter**

4) Histamine receptors

H₁, H₂, H₃ & H₄ and all of them are G-protein coupled receptors

Receptor	Site	Effect	Agonist	Antagonist
H ₁	1. Smooth muscles 2. Endothelium 3. Sensory nerves 4. Brain 5. Adrenal medulla	- Contraction - Vasodilatation - itching, pain - Wakefulness , ↓ appetite - ↑ AD & NA	2-methylhistamine Betahistine	Mepyramine .. H ₁ blockers as Diphenhydramine
H ₂	1. Stomach 2. Heart 3. Brain 4. Uterus 5. Blood vessels	- ↓ HCL - Stimulation - Contraction - Vasodilatation	4-methylhistamine Betazole	Ranitidine Famotidine ... H ₂ blockers
H ₃	1. Presynaptic neurons 2. Brain	Closure of Ca ⁺² channels → ↓ Ca ⁺² influx → sedation	α-methylhistamine	Thioperamide Clophenpropate
H ₄	1. CNS 2. Neutrophils	WBCs involved in tissue repair	Clophenpropate Clozapine	Thioperamide

5) Pharmacological actions

1. Effect on smooth muscles

- Contraction of intestinal and bronchial muscles (bronchoconstriction) (H₁)
- Contraction of the uterus (H₂)

2. Secretory effects

Histamine stimulates parietal cells in the stomach to secrete HCl (H₂)

3. Stimulation of sensory nerves

Pruritus and pain (H₁)

4. Effect on CVS

- **Vasodilatation** (H₁, H₂) → peripheral resistance → **hypotension**
- **↑ Heart rate** (tachycardia / positive chronotropic effect) → baroreceptor mediated (because of hypotension !) (H₂)
- **↑ Force of contraction of the heart** (positive inotropic) → due to ↑ Ca⁺² influx (H₂)
- **Anaphylactic shock ! (histamine is the autacoid of allergy / anaphylaxis) due to:**
 - a. Hypotension
 - b. increased vascular permeability and decreased blood volume

Tripple response phenomenon (Wheal and flare response)

• Happens upon :

- I. intradermal injection of histamine
 - II. drug induced allergy
 - III. insect bites
1. **Red spots / erythema** → local redness of the skin due to **capillary dilatation**
 2. **Red irregular flare** → redness becomes wider due to **more vasodilatation**
 3. **Wheal** → swelling / localized edema due to **increased vascular permeability + itching** due to stimulation of sensory nerves

3) Release of histamine

1. immunological response

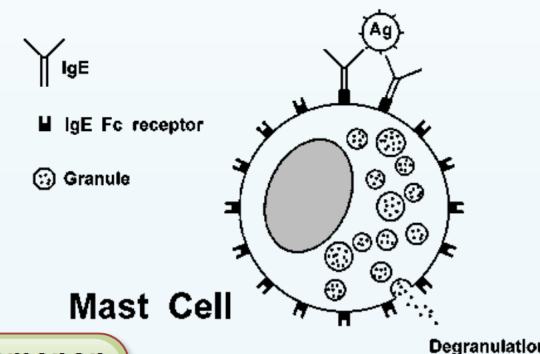
Antigen- Antibody (Ag-Ab) reaction
IgE binds to Ag on the surface of mast cells → causes Ca⁺² influx → **mast cell degranulation** → histamine release → leading to **allergic reaction** such as asthma , rhinitis , itching , increased respiratory tract secretions

2. Chemical release

Allergic reactions due to chemical substances such as
Chocolate , Milk , Egg , Snake venome , Bee venom , drugs (morphine , d-tubocurarine)

3. Mechanical release

Trauma .. causes damage to mast cells



- As we see, most of histmine actions are undesired due to **allergy** or **over secretion of HCl in the stomach**
- So, we would use drugs that oppose these action !
- Drugs are classified to

- **H₁ blockers** (to treat allergy)
- **H₂ blockers** (to treat over HCl secretion)
- **Mast cell stabilizers** (release inhibitors → to prevent allergy)
- **Adrenaline** (Histamine physiological antagonist)

Clinical and diagnostic uses of Histamine

1. Testing gastric secretory function (Augmented histamine test)

- Histamine as S.C injection is used to test the ability of the stomach to secrete HCl
- Possibilities of the test's result may be:**
 - 1) increase in gastric acid secretion **within limits for healthy subjects**
 - 2) **Subnormal increase in HCl secretion** due to defect in the gastric parietal cells (ex. achlorhydria) → **pernicious anemia** due to deficiency of the intrinsic factor secreted by the parietal cells which is necessary for vitamin B₁₂ absorption
 - 3) **Hypersecretion of HCl** such in case of **gastric ulcers or Zollinger-Ellison syndrome**

Histamine substitutes for testing gastric function

Betazole

- isomer of Histamine
- has selective effect on gastric acid secretion

Pentagastrin

- Fully synthetic pentapeptide
- More potent** as gastric secretagogue than histamine and betazole so replaced them for testing gastric function

2. Desensitization (as a treatment)

- This is done by injection of a small dose of histamine
- Followed by gradual increase in the dose over a long period of time
- by this procedure patient becomes insensitive to histamine
- Used in:** Allergic reactions - allergic rhinitis - urticaria - vascular headache (migraine)

3. Testing the integrity of sensory nerves

Histamine stimulates the sensory nerve endings produces **pain and itching**

4. Diagnosis of pheochromocytoma

- in normal cases histamine decrease blood pressure
- pheochromocytoma increase blood pressure due to release of AD and NA

First generation H₁ receptor blockers

Diphenhydramine (Dramenex®)
 Dimenhydrinate
 Chlorpheniramine (Allergex® - Anallerge®)
 Pheniramine (Avil®)
 Promethazine
 Hydroxyzine (Atarax®)
 Clemastine (Tavegyl®)
 Meclizine (Dizirest B₆® - Navidoxine® - Navoproxine®)

indications

Treatment or prevention of symptoms of allergy

Non-histamine receptor mediated effects !

First generation antihistaminics may block other receptors → **muscarinic cholinergic receptors, α receptors and serotonin receptors**

Effects of first generation antihistaminics

1. Sedation (Common side effect "SE")

- As they can cross BBB
- So, can be used as sleep aids (hypnotics)
- Beneficial in psychic allergy
- Not suitable for day use

2. Antiemetic, Antinausea

to prevent **motion sickness** (as prophylaxis)
 Mostly dimenhydrinate and meclizine are used for this purpose

3. Anticholinergic effects (Atropine-like actions) ! "SE"

- **blurred vision** (loss of accommodation to near vision)
- **dry mouth**
- **urine retention** (so contraindicated in patients with benign prostatic hyperplasia)
- **constipation**
- ↑ **IOP** (so contraindicated in patients with glaucoma)

4. α adrenergic blocking effects

This causes postural / orthostatic hypotension **"SE"**

5. Serotonergic blockade

ex. Cyproheptadine (can cross BBB)

H₁ receptor blockers

- They are called antihistaminics
- used to treat allergy
- Classified into:**
 1. First generation antihistaminics
 2. Second generation antihistaminics
 3. Third generation antihistaminics
- Both categories are :**
 - Active orally
 - Metabolized in liver by Cytochrome P₄₅₀
 - They are reversible competitive antagonists of histamine on H₁ receptors
 - With an average duration of action:**
 1. 1st generation → 4-6 hrs except **meclizine** (24 hrs)
 2. 2nd generation → 12 - 24 hrs

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Pharmacokinetics

- Most H₁ receptor antagonists are given orally
- Well absorbed from the GIT and widely distributed
- 1st generation** has high lipid solubility so can penetrate BBB and cause sedation
- 2nd generation** can not pass BBB so does not cause sedation
- Excreted in breast milk** so can cause sedation of the baby
- Metabolized in liver and excreted in urine



Note that **"Caffeine"** may be added to counteract the sedative effect

Second generation H₁ receptor blockers

Cetirizine (Zyrtec® - Histazine-1®)
 Levocetirizine (Levcet® - Xaltec®)
 Loratidine (Claritin®)
 Astemizole
 Acrivastine
 Terfenadine (Fastel®)
 Fexofenadine (Telfast® - Allerfen®)

Advantages

- More selective to H₁ receptors so they will cause less or no**
 - Anticholinergic effects
 - Hypotension
 - Antiemetic effect (less side effects)
- They do not cross BBB** → less sedation
- Longer duration of action (24 hrs)**

Disadvantages

- More expensive**
- Drug-Drug interaction** → Terfenadine and Astemizole may cause life threatening arrhythmia **so contraindicated with** patients receiving cytochrome P₄₅₀ enzyme inhibitors (ex. **Ketoconazole - itraconazole antifungal drugs**) → that would ↓ metabolism → so ↑ level of Terfenadine and Astemizole → causing toxicity (arrhythmia)
- # Fexofenadine** is a metabolite of terfenadine which does not cause arrhythmia (**safer**)

Therapeutic uses of H₁ blockers

1. Allergic rhinitis
 2. Dermatitis
 3. Bronchial asthma (but not effective as monotherapy)
 4. Motion sickness and vertigo (1st generation only)
 5. Sleeping aid in case of insomnia (1st generation only)
- # 1st generation is more effective in allergy

Third generation H₁ receptor blockers

Ebastine (Evastine®)
 Has the least side effects



Mast cell stabilizers (Chromone medications)

They stabilize mast cell inhibiting its degranulation so, inhibit histamine release

HOW?

by blocking Ca^{+2} channels in mast cells so, inhibit Ca^{+2} influx needed for mast cell degranulation

SO!

used to prevent (**prophylaxis**) allergic reactions and not effective in acute attacks (*Histamine is already released!*)

Examples

1. **Nedocromil** → used for allergic conjunctivitis → as eye drops

2. **Ketotifen** (Ketoti®) → applied orally has also H_1 blocking effect so, it is an **antihistaminic and mast cell stabilizer**



3. **Cromolyn sodium**, used in :
a) Allergic rhinitis and Hay fever → as nasal spray
b) Allergic conjunctivitis → as eye drops
c) Bronchial asthma → as inhalation
→ in this case it is used to prevent episodes of bronchial asthma but not used in acute attacks of asthma (*just for prophylaxis*)



Mechanism of action

in presence of HCl sucralfate forms an **insoluble complex** that **adhere to ulcerated tissues** (**Protective coating of the ulcer**)



H₂ receptor blockers

Cimetidine (Not used now)
Ranitidine (Zantac® - Rani® - Ranitidine®)
Famotidine (Famotin® - Famotak®)
Nizatidine (Ulcfree®)

Mechanism of action

Selective competitive antagonists at H_2 receptors so they ↓ **cAMP** leading to ↓ secretion of all gastric secretagogues (*Histamine, Gastrin and Ach*) → ↓ **HCl secretion**

Therapeutic uses

1. **Peptic ulcer** (can be esophageal, gastric or duodenal)
2. **Heart burn** (hyperacidity) الحموضة
3. **Gastro-esophageal reflux disease (GERD)**
(due to incomplete closure of esophageal sphincter of the stomach the acidic content of the stomach contact with the esophageal walls leading to pain)
4. **Zollinger-Ellison syndrome**
(Adenoma / tumor in pancreas leading to ↑ amount of gastrin → ↑ HCl secretion)

Side effects

Cimetidine > Ranitidine > Famotidine > Nizatidine

1. Cimetidine inhibits Cytochrome P₄₅₀ (LME inhibitors)

So, it ↓ metabolism of co-administered drugs and that would be dangerous and may cause toxicity in case of low therapeutic index drugs → such as Warfarin, Phenytoin and Theophyllin.. etc

2. Antiandrogenic effect

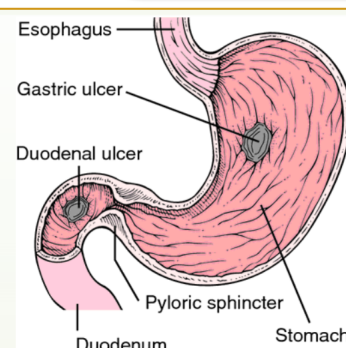
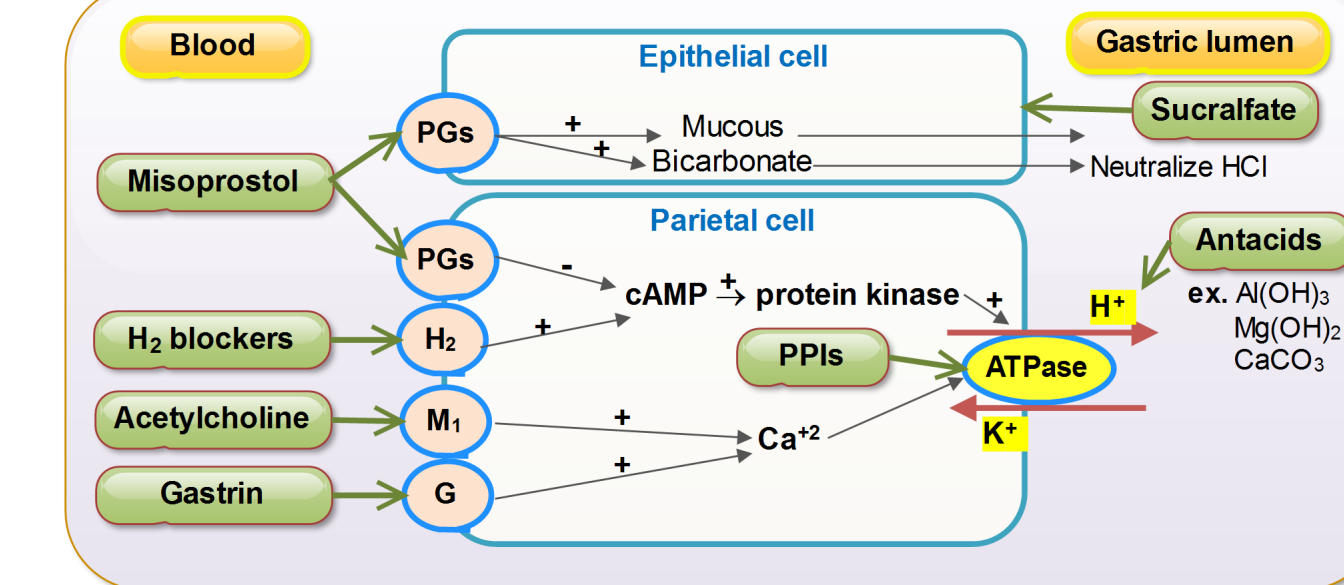
Cimetidine can antagonize the action of androgenic hormones (male sex hormones) causing:

- a. impotence (*decreased sexual ability*)
- b. gynecomastia (*increased breast size in males*)

3. CNS effects

Confusion and slurred speech specially in elderly as cimetidine can pass BBB

4. Cimetidine can pass placenta so not used in pregnant women



Treatment of peptic ulcer

1. H₂ receptor blockers

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2. Proton pump inhibitors (PPIs)

3. Prostaglandin E₁ (PGE₁) analogue

Contraindicated in pregnant women as it causes abortion

Misoprostol (Misotac® - Cytotic®)

Side effect
Mild diarrhea

Mechanism of action

1. increase mucin and bicarbonate production (**Cytoprotection**)
2. decrease HCl production

Gastrofai®

4. Sucralfate

Complex synthetic salt of sucrose and aluminium octasulphate

5. Antibiotics

Amoxicillin, Metronidazole

Antibiotics eradicate **Helicobacter pylori** (this bacteria produces NH_3 , destructing mucin layer and expose stomach tissues to HCl) → so we can prevent the relapse of peptic ulcer

Omeprazole (Omez® - Omepak® - Gasec® - Gastroloc® - Napizole® - Losec® - Healsec®)
Lansoprazole (Zollipak®)
Pantoprazole (Controloc® - Protifix® - Pantoloc® - Antopral® - Pantazol®)
Esomeprazole (Nexium®)

Mechanism of action

They bind irreversibly to proton pump (acid pump) of parietal cells " H^+ / K^+ ATPase system " so they prevent exchange of H^+ with K^+ → leading to ↓ HCl in gastric lumen



2. Serotonin (5-hydroxytryptamine) (5HT)

It is mainly found in CNS and GIT

Synthesis

Hydroxylase

Decarboxylase

Tryptophan (amino acid) → 5-hydroxytryptophan → 5-hydroxytryptamine

Storage and distribution

Serotonin is found in

1. GIT (90%)

it is stored in **enterochromaffin cells** which are scattered between mucosal cells of the gastrointestinal tract particularly between stomach and small intestine

2. CNS (5%)

Serotonin act as a **neurotransmitter** in CNS

3. Platelets

They are loaded with serotonin as they pass through the intestinal circulation
When the platelets bind to a clot they discharge serotonin where it serves as a vasoconstrictor

Metabolism

Serotonin is metabolised by **Monoamine oxidase (MAO)**

MAO

5-hydroxytryptamine → 5-hydroxyindole acetaldehyde → 5-hydroxyindole acetic acid (5HIAA) → **excreted in urine**

High amount of 5HIAA in urine indicates that there is **carcinoid tumor** → which is malignant tumor in enterochromaffin cells of GIT
so it can be used as a diagnostic tool to detect carcinoid tumor (*beside high amount of serotonin in blood*)

- **Symptoms** → Flushing - intestinal colics - diarrhea - bronchoconstriction

- **Diagnosis** → increase 5HIAA in urine about 20 folds

- **Treatment** → Cyproheptadine and Methysergide

Administration of MAOI decreases the excretion of 5HIAA so may lead to **false negative** results for carcinoid

Bananas - Chocolates contain high serotonin concentration may lead to **false positive** results

3) Physiological functions actions

1. Stimulation of GIT motility (**prokinetic effect**)
2. **Vasotonic effect**
3. **Platelet aggregation**
4. **CNS:** 5-HT is involved in
 - mood (↓ 5-HT in brain causes depression)
 - sleep (induction of sleep 5-HT is precursor for **melatonin** by **acetylase enzyme**)
 - reduce of appetite
 - temperature regulation
 - control blood pressure
 - **vomiting** (stimulation of CTZ via 5-HT₃ receptors)

1) Serotonin receptors

Receptor	Site	Main effects	Agonist	Antagonists	Uses
5HT ₁	- Presynaptic CNS - Cerebral blood vessels - Peripheral blood vessels	- Behavioral effects - Cerebral vasoconstriction - Vasoconstriction	- Buspirone (partial agonist) - Ergotamine (partial agonist) - Sumatriptan		
5HT ₂	1. Smooth muscles 2. Cerebral blood vessels 3. Peripheral blood vessels 4. CNS 5. Platelets	- Contraction - Vasodilatation - Vasoconstriction		- Cyproheptadine - Methysergide - Ketanserin - Resperidine	- Carcinoid tumor - Migraine prophylaxis - Hypertension - Antipsychotic
5HT ₃	1. CTZ (chemoreceptor trigger zone) in the brain 2. Sensory nerves	Emesis	5-methyl-5HT	- Ondansetron - Granisetron	- Antiemetics in cancer chemotherapy
5HT ₄	1. CNS 2. Enteric nerves 3. Heart	- ↑ GIT motility - ↑ HR	- Metoclopramide - Cisapride - Tegaserode		- GIT disorders (ex. irritable bowel syndrome)

2) Pharmacological actions

1. Effect on CVS

1. **Vasoconstriction** (5HT₁ - 5HT₂ receptors)
2. **Vasoconstriction of cranial blood vessels** (5HT₁)
(note that dilatation of cranial blood vessels causes headache)
3. **Vasodilatation of skeletal muscles blood vessels and skin** (due to stimulation of 5HT₁ in their blood vessels causing release of **NO** → vasodilatation)
4. **Heart**: +ve inotropic and +ve chronotropic effects **which increase cardiac output**
(this effect is masked by CNS effects → ↑ parasympathetic outflow → ↓ HR)
5. **Blood pressure: IV infusion of 5-HT gives triphasic response:**
 - Initial transient fall in blood pressure
 - Rise in blood pressure due to constriction of large blood vessels
 - Fall in blood pressure due to dilatation of skeletal muscle blood vessels
6. **Induces platelet aggregation** (5HT₂)

2. Nervous system

5-HT₃ receptors in GIT and vomiting center in the brain → **vomiting**

3. Stimulation of sensory nerves

Contributes in **pain** responses (5HT₃)
causes pain when injected intradermally

4. Effect on smooth muscles

1. **Bronchoconstriction**
2. **Contraction of uterus**
3. **GIT:**
 - Contraction of GIT smooth muscles peristalsis (5-HT₂)
 - 5-HT₄ receptors in GIT → ↑ Ach release → **prokinetic** (↑ GIT motility)

5. Effect on CNS

Serotonin is a neurotransmitter involved in:

1. Behavior and mood
2. Attention
3. Appetite
4. Temperature regulation
5. Regulation of blood pressure
6. Stimulation of CTZ leading to vomiting
7. Sleep-wake cycle

So serotonin have been linked to a list of conditions specially in CNS such as Depression, Autism, Anxiety, Obsessive compulsive disorder, Panic attacks

Serotonin receptor **agonists**

5HT_{1A}

Buspirone

Partial agonist → anxiolytic
(used to treat anxiety)



5HT_{1D}

Sumatriptan

Used in the treatment of acute attack of migraine headache (unilateral headache + aura (nausea - vomiting and photophobia))

1. Reverse cranial vasodilatation by selectively stimulating 5-HT_{1D} receptors → **cerebral vasoconstriction**
2. It blocks the neuropeptide mediated inflammatory response that occurs after trigeminal nerve stimulation



Each migraine attack has two phases

1. **First phase** → cerebral vasoconstriction and ischemia → **aura** → nausea, vomiting and photophobia
2. **Second phase** (longer) → vasodilatation → **pain and headache** - in this phase trigeminal neurons release inflammatory mediators → vasodilatation and inflammation → stimulation of nociceptive fibers pain

5HT₄

Cisapride

It inhance (increase) GIT motility (Prokinetic drug) by two ways

1. by being a 5HT₄ receptors agonist (Normally when serotonin stimulate 5HT₄, Ach release increase → increase GIT motility)
2. increase Ach release from myenteric nerves → increase GIT motility

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Therapeutic uses

1. Treatment of gastroesophageal reflux disease (GERD) by :
a) increase lower esophageal sphincter tone / pressure
b) Prokinetic action
2. Irritable bowel syndrome (at constipation time)

Tegaserod

- is a new drug that is more selective agonist at 5-HT₄ receptor
- **used to** treat irritable bowel syndrome

Treatment of acute attacks of migraine

Sumatriptan - Ergotamine

Prophylaxis

Methysergide

Note

LSD (lysergic acid diethylamide) is a potent 5-HT₂ receptor agonist in the brain causes hallucinations

Selective serotonin reuptake inhibitors (SSRIs)

Discussed in details in CNS

Fluoxetine
Paroxetine
Fluvoxamine
Sertraline
Citalopram

Therapeutic uses

Treatment of depression by inhibiting reuptake of 5HT so, serotonin level in synapse increase

Advantages of SSRIs

No effect on Noradrenaline uptake so, devoid of side effects of other antidepressants (ex. tricyclic antidepressants)

Serotonin receptor **antagonists**

5HT₂

Ketanserin

- It also blocks α_1 and H₁ receptors
- **Treatment of** hypertension and Raynaud's disease

Risperidone

- Originally it is D₂ receptors antagonist
- It also blocks 5-HT₂, α_1 and H₁ receptors
- it is **atypical antipsychotic** so, used in the treatment of positive and negative symptoms of schizophrenia



Cyproheptadine

- it also blocks H₁ receptors and anticholinergic effects
- Treatment of carcinoid tumors, allergy and urticaria, sedative and **appetizer** for children



Methysergide

- It causes vasodilatation
- **Used in** prophylaxis of migraine (action starts after 1-2 days) and carcinoid tumor (to treat diarrhea)

5HT₃

Ondansetron - Granisetron

- Block 5HT₃ receptors in **stomach and CTZ** → so, inhibit vomiting
- Used as **antiemetic** specially in cancer patients (prevention of chemotherapy and radiation induced vomiting) and pregnant women



Types of NOS

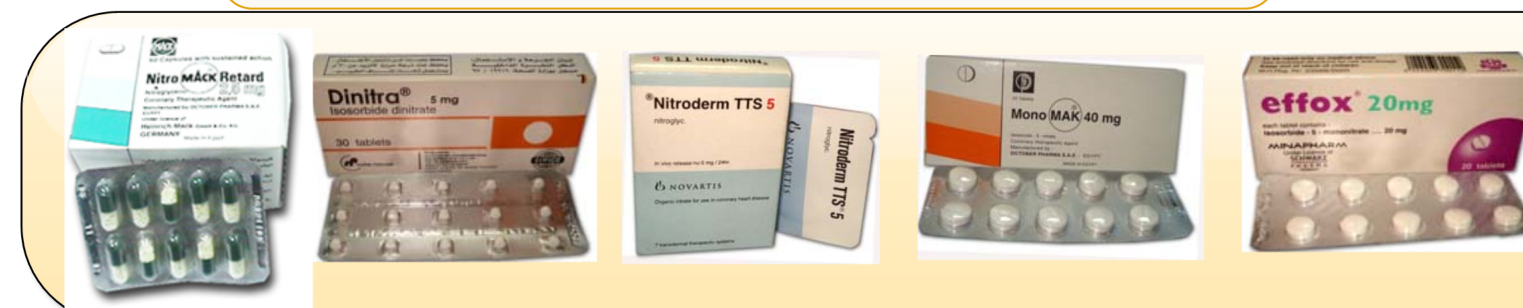
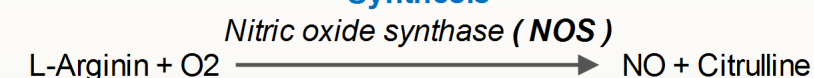
There are three isoforms of NOS

NOS	Type	Site	Function
1. nNOS (neuronal) NOS I	Constitutive (Constitutional)	1. Brain 2. Peripheral neurons	NO is a neurotransmitter
2. iNOS (inducible) NOS II	inducible (induced by infection)	1. Macrophages 2. Smooth muscles 3. Cardiac cells	immune function → cytotoxic (eradicates infection)
3. eNOS (endothelial) NOS III	Constitutive	1. Endothelium of blood vessels 2. Cardiac cells	NO causes vasodilatation so, regulate vascular tone and blood supply to organs

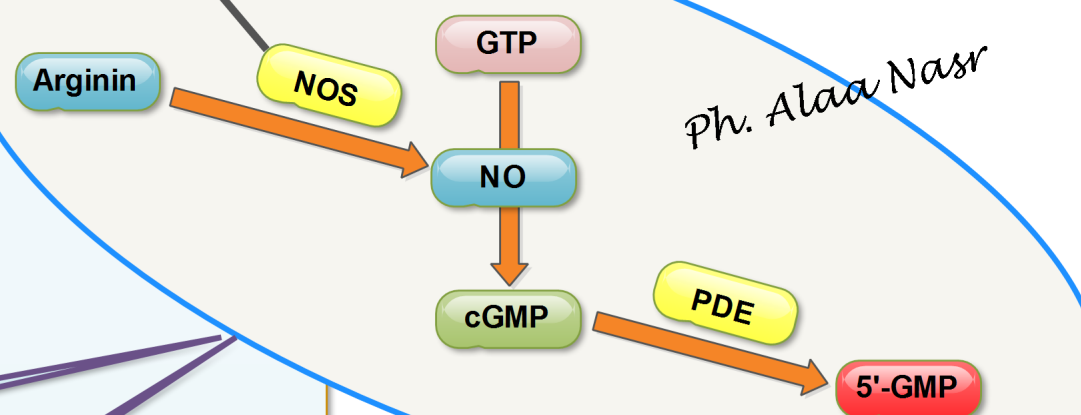
3. Nitric oxide (NO)

1. NO is also known as **endothelial derived relaxing factor (EDRF)**
2. It is produced **denovo** (just before performing its action) in endothelial cells

Synthesis



Mechanism of action



Pharmacological modulators of NO

1. NO donors

Nitroglycerine - Nitrates - Nitrites

Vasodilators → so, used in **angina pectoris** (coronary heart disease)

2. Phosphodiesterase inhibitors

Causes accumulation of cGMP → modulating vasodilatation effect

a) PDE-5 inhibitors

Sildenafil (Viagra®) - Tadalafil (Cialis®)

Exerting **vasodilatation in penis** leading to erection so, can be used to treat **erectile dysfunction**

b) PDE-1 inhibitors

Vinpocetine (Cavinil®)

- Have **cerebral blood flow enhancing** and neuroprotective effects
- **Used in** the treatment of cerebrovascular disorders and age-related memory impairment

c) Methylated xanthenes such as **Caffeine**, **Aminophylline**, **Pentoxifylline** (Trental® - Pental®) and **Theobromine** are considered as **non-selective PDE inhibitors**

3. Inhibitors of NOS enzyme

Arginine analogues

- Bind to Arginin binding site in NOS enzyme leading to its inhibition
- **Not used clinically**, only used as a research tool

Actions

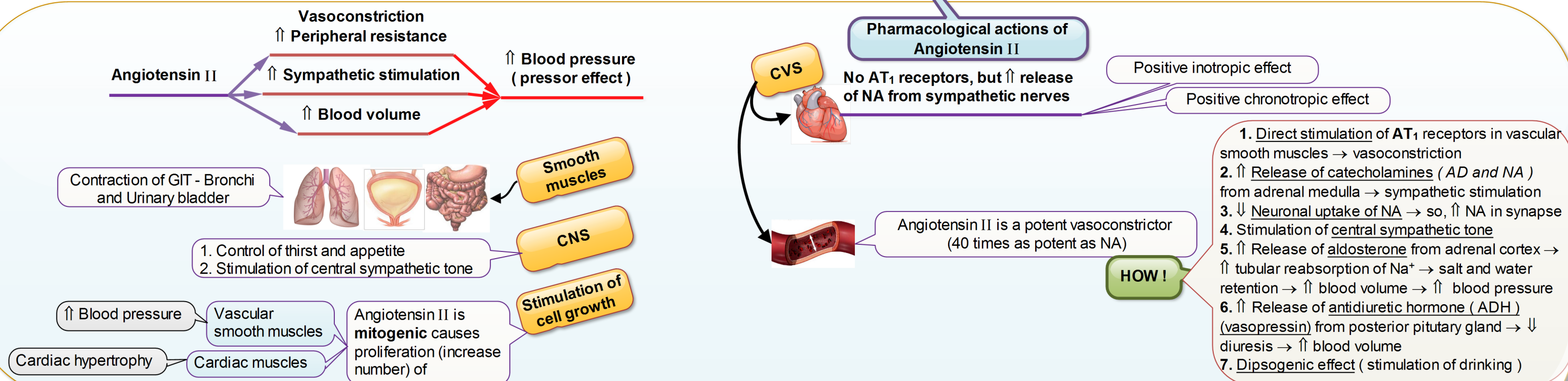
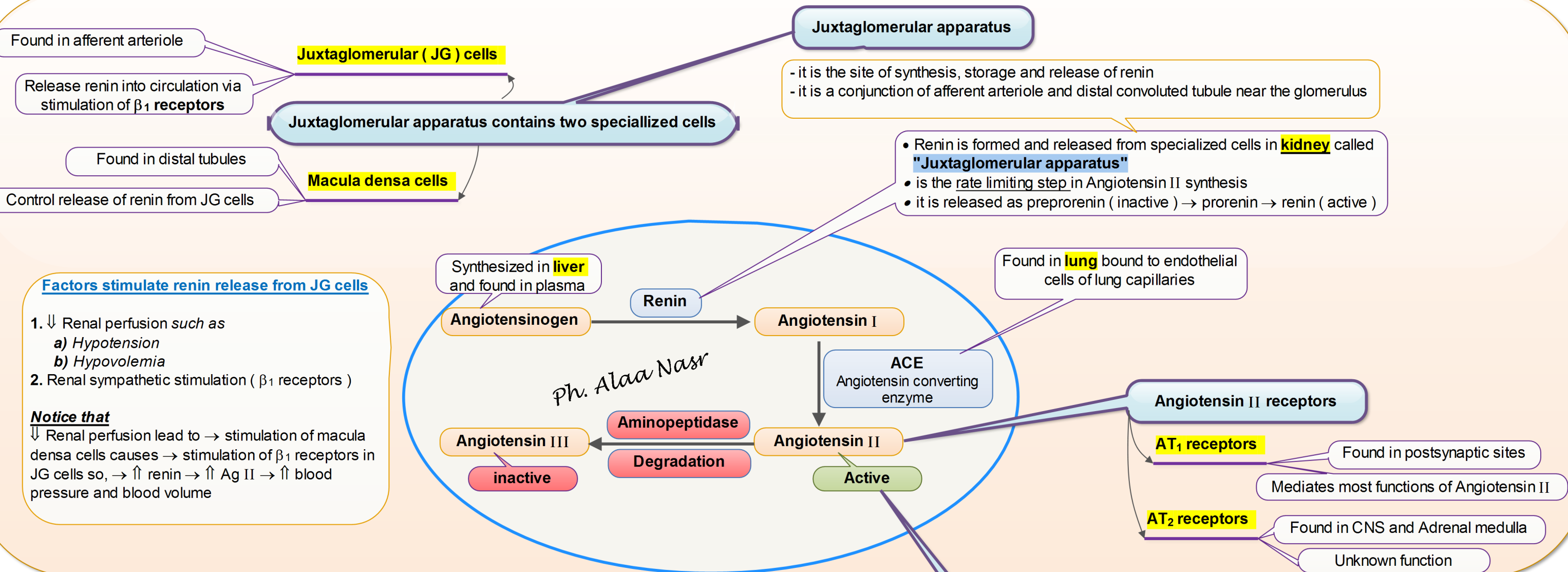
1. Smooth muscle relaxation and vasodilatation
2. Inhibition of platelet aggregation

Degradation of cGMP

Degraded by **phosphodiesterase enzymes (PDE)** to **5'-GMP** (which is inactive) leading to termination of action of NO



4. Angiotensin II and Renin - Angiotensin system



Inhibitors of renin - angiotensin system

- RAS is involved in the pathogenesis of hypertension
- **RAS can be inhibited by:**

1. inhibitors of renin release

Renin is released from JG cells in response to β_1 stimulation

So, renin release can be inhibited by:

1. β blockers..
ex. **Propranolol**
2. Centrally acting sympatholytics..
ex. **Clonidine - α methyl dopa**

- Because of non-selectivity there will be many side effects
- Also their effect on the heart is much more prominent than on renin release

- Because of non-selectivity there will be many side effects
- Also their effect on the heart is much more prominent than on renin release

 You should know
α **methyldopa (Aldomet®)** is the safest antihypertensive drug during pregnancy



**Pictures of drugs in
"Hypertension" lecture**

2. inhibitors of renin activity

ex. Enalkiren - Remikiren

- # There is now **Aliskiren (Tekturna®)** which is an **effective** direct renin inhibitor

3. Angiotensin converting enzyme inhibitors (ACE inhibitors)

ex. Capotril - Enalapril - Lisinopril - Quinapril

Mechanism of action

Dual mechanism

Decrease activation of angiotensin II

Decrease vasoconstriction

inhibit degradation of **bradykinin**

Vasodilatation

Decrease
vasoconstriction

Vasodilatation

Effect of ACE

4. AT₁ receptor antagonist

Mechanism of action

Competitive antagonists of Angiotensin II
on AT₁ receptors

Examples

Saralasin

But not used clinically now because

1. it has short half life
2. it is partial agonist
3. it must be given parenterally as it is a peptide

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2. it is partial agonist
3. it must be given parenterally as it is a peptide

Losartan - Valsartan - Candesartan

1. Pure antagonist
2. Can be given orally as they are not peptides
3. No cough as there is no effect on bradykinin

Therapeutic uses

Treatment of hypertension

Adverse effects

- ### 1. Dry (non-productive) cough

- due to **accumulation of bradykinins**
- may require discontinuation of the drug

- ## 2. Angioedema

edema of skin, mucous membrane and SC tissues, it is **rare** (< 1%) but dangerous specially edema in larynx and tongue

- ### 3. Category C in pregnancy

ACE inhibitors are **teratogenic** (may cause fetal malformations) so, they are contraindicated during pregnancy

- #### 4. Renal impairment

Not administered for patients having **diseased kidneys**, or taking another renal impairing drug (**ex. Aspirin**)

Angiotensin I

inactive

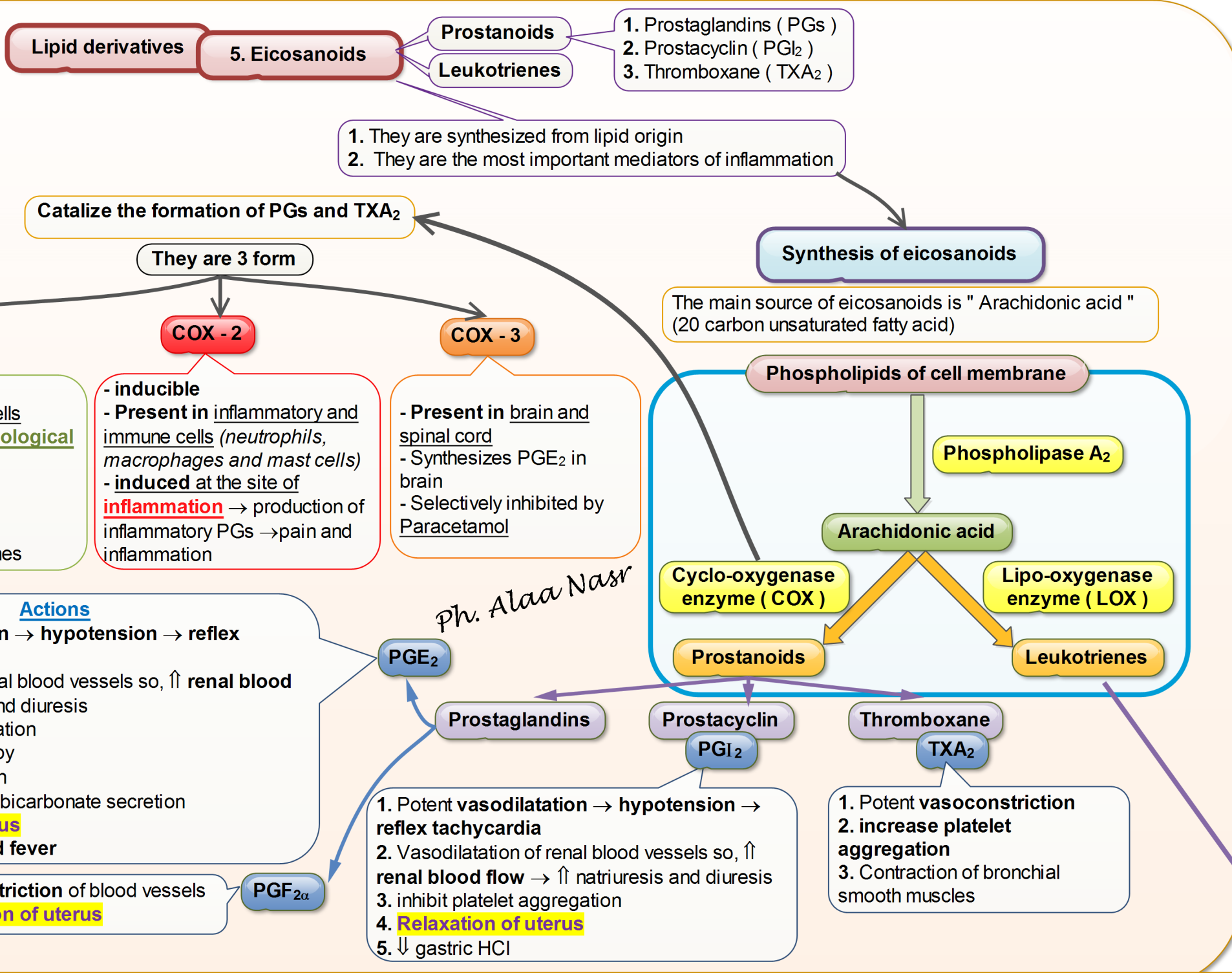
Bradykinin

Vasodilator

**ACE (Angiotensin converting enzyme)
(Kininase II)**

Angiotensin II

inactivation



Clinical uses of prostaglandins (PG analogue)

Dinaprostone (PGE₂ analogue)
Carboprost (PGF_{2α} analogue)

Uses
induction of labour or abortifacients

Misoprostol (PGE₁ analogue)

Uses
1. Treatment of **gastritis** and **peptic ulcer**
misused to induce abortion illegally so, **contraindicated in** pregnancy



Alprostadil (PGE₁ analogue)

Uses
1. **impotence** (induces vasodilatation → erection)
2. used for neonates with **congenital heart defects / Pulmonary hypertension** (induces vasodilatation in patent ductus arteriosus (PDA) (bridge between aorta and pulmonary artery))

- LTs are produced from arachidonic acid metabolism by Lipo-oxygenase enzyme
- They are present in lungs, platelets, mast cells , leukocytes

Types of LTs
LTA₄ - LTB₄ - LTC₄ - LTD₄ - LTE₄ - LTF₄

Pharmacological actions

1. Vasodilatation → hypotension → reflex tachycardia
2. LTC₄ and LTD₄ causes **severe bronchoconstriction** (1000 times mor than Histamine !)
3. increase microvascular permeability leading to **mucosal edema**

You should know
LTs are involved in the pathology of airway diseases such as bronchial asthma

Pseudo allergy (Aspirin asthma) (NSAIDs-induced asthma) !

- Aspirin inhibit both COX-1 & COX-2
- So, more arachidonic acid will be converted to leukotrienes → leading to severe bronchoconstriction (asthma)

Leukotriene modifiers
Zileuton
- Lipo-oxygenase inhibitor decrease LTs
- Was used in asthma, **but now it is prohibited**

Zafirlukast and Montelukast
- Leukotriene (LTD₄) receptor antagonist
- is used in asthma



Clinical uses of prostaglandins inhibitors

Anti-inflammatory drugs

1. Corticosteroids
2. NSAIDs

1. Corticosteroids

inhibit phospholipase A₂
→ so decrease synthesis of both eicosanoids and leukotrienes (PGs & LTs)

2. Cyclo-oxygenase inhibitors

Non steroidal anti-inflammatory drugs NSAIDs

Non selective

inhibit both COX-1 & COX-2, so **beneficial effects of COX-1 on gastric mucosa, platelets and kidneys are lost!**

Examples

Aspirin (acetyl salicylic acid)
Diclofenac
Ketoprofen
Ibuprofen
Indomethacin
Piroxicam

Side effects

1. Nephrotoxic
2. Gastritis



Therapeutic uses

1. Analgesic (↓ pain)
2. Antipyretic (↓ fever)
3. Anti-inflammatory
4. Anti-platelet aggregation (such as aspirin 75 mg)

Paracetamol

1. Selective inhibitor for COX-3 and has no significant action on COX-1 and COX-2 this may explain its lack of anti-inflammatory action
2. it has no GIT side effects



You should know Aspirin doses

75 mg used in anti-platelet aggregation
300 mg used as analgesic



Selective COX-2 inhibitors

inhibit COX-2 with little or no effect on COX-1 so, have little gastric and renal side effects

Examples

1. Celecoxib

2. Rofecoxib .. its use is **prohibited** due to its serious side effects on the heart

